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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,637	08/07/2001	Lawrence J. Marnett	N-6138 RSM	2070

7590 07/14/2004

Richard S. Myers, Jr.
Stites & Harbison, PLLC
424 Church Street Suite 1800
Nashville, TN 37219

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,637	MARNETT ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-27,29-39 and 87-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-8,10-22 and 39* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) *37 and 38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Apr 23, 2004 has been entered.

Please note that the examiner assigned to this application has changed.

Claim 23 has been amended. Claims 87-89 have been added. Claims 1-8, 10-27, 29-39 and 87-89 are pending and under consideration.

Text of sections of Title 35 US Code not found in this action can be found in a previous Office action.

Claim 89 is objected to for the omission of the preposition "in" before the word "need".

Claims 23-27, 29-32, 36 and 87-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The recitation of "the amount" in claim 36 lacks antecedent basis in claim 33. For purpose of examination claim 36 will be considered as dependent upon claim 35.

(b) The recitation of "the subject" in claim 23 lacks antecedent basis within the claim.

(c) Claim 24 lacks an active method step relating the measurement of the amount of metabolite in the sample with the method of detecting an activity of COX-2 as recited in the method objective of claim 23.

(d) Claim 25 lacks an active method step relating the activity of the COX-2 enzyme with the method of detecting the COX-2 enzyme as recited in the preamble of claim 23.

(e) The recitation of "the measuring step" in claim 29 lacks antecedent basis in claim 23.

(f) Claim 35 lacks an active method step relating the measurement of the amount of metabolite in the sample with the method of detecting an activity of COX-2 as recited in the method objective of claim 33.

Claims 23-25, 29-33, 35, 36 and 87-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods of detecting an activity of a COX-2 enzyme in a patient or a sample comprising detecting a metabolite of a COX-2 selective substrate. Thus the instant method claims are reliant upon a genus of COX-2 selective substrates. A COX-2 selective substrate is a substrate metabolized only by COX-2. Thus the genus upon which the instant method claims rely encompasses any molecule which would be metabolized by COX-2 relative to other COX enzymes, such as COX-1. The instant specification discloses only 2-arachidonylglycerol as a COX-2 selective substrate

The genus is highly variant because it includes molecules which differ widely in structure and function from 2-arachidonylglycerol and includes synthetic molecules which are not derivatives of native substrate of COX-2, such as arachidonic acid. The disclosure of 2-arachidonylglycerol fails to describe the genus encompassed by the claims because said genus includes molecules which differ widely in structure and function from 2-arachidonylglycerol. The disclosure of 2-arachidonylglycerol does not provide an adequate written description of a genus of COX-2 selective substrates on which the instant method claims depend.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the

claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not

adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of COX-2 selective substrates, per Lilly, by structurally describing a representative number of COX-2 selective substrates or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a genus of COX-2 selective substrates in a manner that satisfies either the Lilly or Enzo standards. The specification provides the complete structure of only one COX-2 selective substrate, and does not provide any partial structure responsible for COX-2 selectivity, nor any physical or chemical characteristics of the COX-2 selective substrates which endow said substrates with specificity for COX-2 versus COX-1, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the prior art teaches that the active site channel of the COX-2 enzyme is larger than that of COX-1 and can accommodate non-carboxylic fatty acyl side chains due to the presence of additional binding site(s) at the bottom of said channel, this does not provide a description of structural requirements for COX-2 selective substrates that would satisfy the standard set out in Enzo.

The specification also fails to describe the genus of COX-2 selective substrates by the test set out in Lilly. The specification describes only a single COX-2 selective substrate. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the genus of COX-2 selective substrates Since the specification fails to adequately describe the product on which the claimed methods rely, it also fails to adequately describe the claimed methods.

Claims 23 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting COX-2 activity in a patient comprising analyzing a sample of urine, plasma, cerebrospinal fluid, saliva, sputum, bile, joint fluid and biopsy tissue, does not reasonably provide enablement for a method of detecting COX-2 activity in a patient comprising analyzing conditioned medium from a cell culture. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 23 is drawn to a method of detecting an activity of a COX-2 enzyme in a patient comprising obtaining a sample of the subject and detecting a metabolite of a COX-2 selective substrate in the sample, wherein the presence of the metabolite in the sample is indicative of COX-2 activity. Claim 32 specifies that the sample is conditioned media from a cell culture. The specification does not provide objective evidence that pathological tissue taken from a patient suffering from a COX-2 related disorder would persist in expressing COX-2 when grown as a cultured cell. It is well known in the art that cells do not retain all of the characteristics of a primary tumor when made to adapt to conditions of growth in cell culture (Freshney, The Culture of Animal Cells, 1994, page 5, under the heading "Major Differences in Vitro" and pages 349-350). Further, it is recognized in the art that the COX-2 enzyme is inducible and regulated by a range of agonists rather than constitutive as the COX-1 enzyme (Kozak et al Journal of Biological Chemistry, 2000, Vol. 275, pp. 33744-33749, Attachment "A" of the response filed X/Y/Z, especially page 33744, first column, line 11 after the abstract to column 2, line 2). Therefore, without specific teachings in the specification, one of skill in the art would reasonable conclude that the expression of COX-2 in pathological tissue in vivo would not have a nexus to the expression of COX-2 in a cell adapted to tissue culture conditions. Thus, one of skill in the art would be subject to under experimentation in order to carry out the instant invention to the extent that the sample is conditioned media from a cell culture.

Claims 33, 35 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al (Journal of Biological Chemistry, 1997, Vol. 272, pp. 21181-21186).

Claim 33 is drawn to a method of detecting COX-2 activity in a sample, comprising adding a COX-2 selective substrate to a sample and detecting a metabolite of COX-2 selective

substrate in the sample wherein the presence of the metabolite indicates that activity of the COX-2 enzyme in the sample. Claim 35 embodies the method of claim 33 further comprising measuring an amount of the metabolite. Claim 36 embodies the method of claim 33 [35] further comprising relating the amount of the metabolite to the activity of the COX-2 enzyme.

Yu et al disclose a method of detecting COX-2 activity in a cell comprising contacting said cell with anandamide and measuring the synthesis of the metabolite PGE E2 ethanolamide as indicative of COX-2 activity by said cell (page 21186, first column 1, line 34 to column 2, line 12).

Claims 23-25, 29-32 and 87-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isakson et al (WO 97/14679) in view of Yu et al (Journal of Biological Chemistry, 1997, Vol. 272, pp. 21181-21186).

Claim 23 is drawn to a method of detecting an activity of a COX-2 enzyme in a patient comprising obtaining a sample of the subject and detecting a metabolite of a COX-2 selective substrate in the sample, wherein the presence of the metabolite in the sample is indicative of COX-2 activity. Claim 24 embodies the method of claim 23, further comprising measuring an amount of the metabolite in the sample. Claim 25 embodies the method of claim 24 further comprising relating the amount of the metabolite in the sample to the activity of the COX-2 enzyme in the subject and relating said amount of the COX-2 specific metabolite to the activity of the COX-2 enzyme. Claim 29 embodies the method of claim 23 wherein the measuring step includes generating a mass spectrum of the metabolite. Claims 30 and 31 embody the method of claim 23 wherein the sample comprises urine and plasma, respectively. Claim 32 embodies the method of claim 23 wherein the sample is selected from cerebrospinal fluid, saliva, sputum, bile, joint fluid, or biopsy. Claims 87 and 88 embody the method of claim 23 wherein the patient is in need of diagnosis or monitoring of an inflammatory disease state, and the presence of cancer, respectively. Claim 89 embody the method of claim 23 wherein the patient is in need of monitoring anticancer therapy.

Isakson et al teach a method of detecting neoplasia in a mammal, including colorectal cancer, and cancers of the breast, cervix, , lung, prostate, bladder and skin as well as various COX-2 associated diseases including arthritis, post-operative inflammation, inflammatory bowel

disease, and pulmonary inflammation (page 11, line 31 to page 12, line 34), thus fulfilling the specific embodiments of claims 87 and 88 drawn to the diagnosis of inflammation or cancer. Isakson et al teach that the method can be used to monitor the course of the inflammation in an individual and the determination of efficacious therapeutic anti-inflammatory treatments (page 12, line 35 to page 13, line 5). Isakson et al teach the above methods wherein the amount of COX-2 activity is measured by the binding of a COX-2 specific agent to COX-2 in vivo (page 3, line 34 to page 4, line 16). Isakson et al teach COX-2 specific agents which bind to and inhibit COX-2 (page 4, lines 20-22). Isakson et al teach that the concentration of the observed agent in tissue is related to the amount of COX-2 in said tissue (page 14, lines 20-22). Isakson et al do not teach the detection of a metabolite of a COX-2 specific substrate.

Yu et al teach a method of detecting COX-2 activity in a cell comprising contacting said cell with C-14 labeled anandamide and measuring the synthesis of the metabolite PGE E2 ethanolamide as indicative of COX-2 activity by said cell (page 21186, first column 1, line 34 to column 2, line 12). Yu et al teach the determination of the mass spectrum of the metabolites of anandamide (page 21184-21185, Figures 4 and 5).

It would have been prima facie obvious at the time the claimed invention was made to administer C14-labeled anadamide to patients in place of the radiolabeled COX-2 specific inhibitors as taught by Isakson et al and to measure the resultant C14 labeled metabolite, PGE E2 ethanolamide, as indicative of COX-2 activity in said patient for the purpose of diagnosing or monitoring cancer, anticancer therapy or an inflammatory disease state. One of skill in the art would have been motivated to do so by the teaching of Yu et al on the specific metabolism of anandamide to PGE E2 ethanolamide by cells expressing COX-2 and the lack of specific metabolism of anandamide to PGE E2 ethanolamide by cells expressing COX-1. One of skill in the art would be motivated to do so because the administration of a C14 labeled compound involves less risk to a patient that the radio isotopes required for in vivo imaging by PET and SPEC as taught by Isakson et al (page 9, lines 5-32).

Claims 37 and 38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/12/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER